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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/530,262

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EXAMINER

WELTER, RACHAEL E

ART UNIT

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/530,262	Applicant(s) KOIKE ET AL.	
	Examiner RACHAEL E. WELTER	Art Unit 1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11/7/08.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 15-25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 15-25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>7/23/08, 9/17/08, 11/6/08</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claim Status

Claims 15-25 are pending. Claims 1-14 are cancelled.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on September 17, 2008, November 6, 2008, and July 23, 2008 were in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. Accordingly, the information disclosure statements were considered by the examiner. A signed copy of forms 1449 are enclosed herewith.

New Rejections

The following rejection constitutes new grounds for rejection necessitated by amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

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2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 15-21, 23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Piper (WO 01/32158) in view of Zhuang et al (*Practical Pharm. Prep. Tech.*, January 1999, p. 203-204) as evidenced by Remington (*Remington: The Science and Practice of Pharmacy*, 21st Edition, 2003, pp. 675-676) and RxList: The Internet Drug List (<http://www.rxlist.com/actos-drug.htm>).

Piper teaches a pharmaceutical formulation which includes a combination of metformin and at least one other antidiabetic agent (pg. 6, lines 28-31), which can be a thiazolidinedione (pg. 14, line 9), such as pioglitazone (pg. 15, line 20). As evidenced by Rx List, Takeda-Lilly-Actos (pg. 15, line 21) mentioned in Piper is a pioglitazone hydrochloride. Piper also teaches that the antidiabetic agent can be glyburide (pg. 8, lines 14-15). Furthermore, Piper teaches that the formulation has at least substantially equivalent efficacy in treating type 2 diabetes as compared to prior art antidiabetic formulations containing metformin, but with substantially reduced side effects (pg. 1, lines 10-14). In forming a low dose metformin hydrochloride and glyburide formulation, the granules are formed by wet granulation of **a mixture of metformin and glyburide** (pg. 23, lines 19-20). More specifically, Piper teaches that a dry mixture of croscarmellose sodium and glyburide were dispersed together followed by blending with the metformin hydrochloride/magnesium stearate in a high shear mixer with an aqueous povidone solution and dried. (pg. 26, lines 1-4). The dried granulation was reduced with a screening mill and mixed with microcrystalline cellulose using a tumble mixer (pg. 26,

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lines 8-10). Magnesium stearate was incorporated as a lubricant using a tumble mixer to produce the final compression blend (pg. 26, lines 10-12). The resultant blend was compressed into tablets and film-coated (pg. 26, lines 13-24). Because the granules are being formed from a mixture of metformin and glyburide and a high shear mixer is used, the reference implies that the biguanide and pioglitazone are uniformly dispersed. Furthermore, Piper teaches that the glyburide has a particle distribution of a 25% undersize value not more than 6 μm , a 50% undersize value (also known as the mass median particle size) 7 to 10 μm , and a 75% undersize value not more than 23 μm (pg. 23, lines 11-15). Piper further conducted a study with particle size data to achieve comparable bioavailability to Micronase (glyburide alone) from the combination product of glyburide and metformin (pg. 26, lines 24-29). According to Piper, the particle size values or particle distribution assured reproducibility of glyburide dissolution and bioavailability from metformin hydrochloride-glyburide tablets.

Piper does not explicitly teach a median particle size of biguanide (metformin) of 10-100 μm or a ratio of median size biguanide particles to median size pioglitazone particles of 0.5 to 15.

However, according to Zhuang et al, a more uniform mixture is obtained by having a small particle size of each ingredient and a similar size of each ingredient (pg. 3, lines 4-5).

Therefore, it would have been obvious to an artisan of ordinary skill at the time the invention was made to have a similar biguanide median size to pioglitazone median size resulting in a 1:1 ratio. One would have been motivated to do so in order to create

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the mixture in Piper more consistent during granulation because Zhuang et al suggest that similar sized ingredients make a more uniform mixture.

Furthermore, as evidenced by Remington and Piper, the particle size of a drug in an oral dosage form can affect its dissolution rates. According to Remington, higher dissolution rates may be achieved through the reduction of the particle size (pg. 675, column 1, "Effect of Particle Size On Dissolution"). Remington further teaches that in the case of cloramphenicol, formulations containing smaller particles (50-200 μm) were absorbed faster than formulations containing larger particles (400-800 μm). Moreover, as taught in Piper, the particle sizes of glyburide were based on achieving a desired bioavailability. Thus, it is well known in the art and it would be obvious to an artisan of ordinary skill to optimize and manipulate the particle sizes based on the desired dissolution rates and bioavailability of the drug.

Regarding claim 21 and the coefficient of variation of the pioglitazone, the examiner has no access to laboratory equipment and burden is put on applicant to prove that the reference teaches otherwise. When the reference discloses all the limitations of a claim except a property or function and the examiner cannot determine whether or not the reference inherently possesses properties which anticipate or render obvious the claimed invention, the examiner can shift the burden of proof to applicant as in *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980).

Regarding claim 23, which is drawn to the dissolution rate of the formulation, this limitation is an intended use for the composition. Because it does not materially impact the structure of the composition itself, it is not given any patentable weight. Because

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the prior art teaches the obvious core structure of the solid formulation of metformin and pioglitazone, the formulation is capable of having the instantly claimed dissolution characteristics when subjected to the Paddle Method depending on the amounts of drug, drug solubility, and median particle size. Further, one of ordinary skill in the art would have been motivated to alter the dissolution characteristics of a drug formulation depending on the needs of a particular patient population.

Claims 22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Piper (WO 01/32158) in view of Zhuang et al (*Practical Pharm. Prep. Tech.*, January 1999, p. 203-204) as evidenced by Remington (*Remington: The Science and Practice of Pharmacy*, 21st Edition, 2003, pp. 675-676) and RxList: The Internet Drug List (<http://www.rxlist.com/actos-drug.htm>) and further in view of *Remington (Remington's Pharmaceutical Sciences, 18th Edition, 1990, pg. 1639) and Kumar (US Patent No. 6,117,451).

*Note: The Remington 18th Edition will be referred to as RPS in the body of this rejection.

The disclosures of Piper and Zhuang et al were discussed above.

Piper and Zhuang et al do not explicitly teach solid preparations having a hardness of 100-400 N.

RPS teaches that the resistance of a tablet to chipping, abrasion or breakage under conditions of storage, transportation, and handling before usage depends on its hardness (column 1, "Tablet Hardness", lines 1-3). According to RPS, a hardness of 4

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kg, which corresponds to approximately 40 N, is considered to be a minimum for a satisfactory tablet.

Kumar teaches a metformin hydrochloride formulation capable of being directly compressed with specific excipients having desired hardness, disintegrating ability, and acceptable dissolution characteristics (column 4, lines 65-67--column 5, lines 1-5). According to Kumar, microcrystalline cellulose is an excipient that is highly compressible and produces hard, strong tablets at a low machine pressure (column 9, lines 18-20). Kumar further teaches that microcrystalline cellulose prevents chipping and capping of the metformin hydrochloride tablets (column 9, lines 20-21).

Therefore, it would have been obvious to an artisan of ordinary skill at the time the invention was made to have a tablet hardness of higher than 40 N. One would have been motivated to do so in order to make a satisfactory tablet that would be resistant to chipping, abrasion or breakage under certain conditions, as suggested by RPS.

Furthermore, as suggested by Kumar, it is known in the art to optimize and manipulate tablet hardness depending on a tablet's excipients and desired dissolution rate. Like Piper (see pg. 26, lines 8-10 of Piper), Kumar teaches microcrystalline cellulose as a preferred excipient and Kumar suggests a desired tablet hardness for metformin hydrochloride. Optimization of parameters is a routine practice that would be obvious to a person of ordinary skill in the art to employ and reasonably expect success. One would have been motivated to determine the optimal amount of each excipient in order to achieve the desired tablet hardness. See *In re Aller*, 220 F.2d 454, 456, 105

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USPQ 233, 235 (CCPA 1955) & MPEP 2144.05. Burden is put on the applicant to prove otherwise and show the criticality of the claimed hardness range.

Response to Arguments

Applicant's arguments filed 11/7/08 have been fully considered but they are moot in view of the new grounds for rejection presented above and unpersuasive in regard to Zhuang et al, which was a reference used in the previous rejection. Accordingly, the examiner will address any arguments presented by applicant which are still relevant to Zhuang et al.

Applicant argues that Zhuang does not teach or suggest having a final product comprising two components with a specific median particle size ratio or median particle sizes, as recited in the present claims. Applicant argues that "median size," as defined in the present application, refers to the particle size that divides crude particles from fine granules at 50%, each in weight distribution or number distribution. Applicant argues that Zhuang teaches "pulverizing" and/or "sieving" and that this method is not used to reach the specific median size ratio and/or the median sizes, as recited in the independent claims and their dependent claims.

In response to applicant's arguments, the examiner agrees with applicant that Zhuang does not teach the specific median particle size ratio or median particle sizes, as recited in the present claims. In this case, the examiner is only using Zhuang as motivation to provide support for using similarly sized particles of metformin and pioglitazone in order to provide a more uniform mixture. The examiner is not using

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Zhuang to compare how the particles sizes are obtained. The examiner is only using the general teaching of Zhuang as motivation to have similar particle sizes of metformin as particle sizes of the anti-diabetic agent (glyburide) taught in Piper.

Conclusion

Claims 15-25 are rejected. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RACHAEL E. WELTER whose telephone number is (571) 270-5237. The examiner can normally be reached 7:30-5:00 Monday-Friday.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached at 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

REW

/Lakshmi S Channavajjala/

Primary Examiner, Art Unit 1611

February 1, 2009